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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,645	08/10/2006	David Salomon	251206	9318

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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,645	SALOMON ET AL.	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-14 and 17-26* is/are pending in the application.

4a) Of the above claim(s) *7-14 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/4/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/4/2009 has been entered.

Formal Matters

This action is in response to paper filed 3/4/2009.

Claims 1, 7-14, 17-26 are pending.

Claims 7-14, 21-26 are withdrawn from consideration.

Claims 1, 17-20 are being examined.

Priority

1. The instant application was filed 8/10/2006 and is a national stage entry of PCT/US04/432649 filed 10/1/2004.

Response to Amendment

2. The declaration under 37 CFR 1.132 filed 3/4/2009 is insufficient to overcome the rejection of claims 1, 17-20 based upon 112-1st paragraph enablement rejection as set forth in the last Office action because: The declaration filed by co-inventor Nancy Berman has not demonstrated the claims are enabled for detecting NeuroAids by

increased expression of SEQ ID NO 1 in central nervous system tissues. The declaration is addressed in the response to arguments of the 112-1st paragraph rejection presented below.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method of detecting NeuroAIDS disease in any mammal comprising assaying the expression level of a SEQ ID NO 1 in the central nervous system of the mammal wherein 2.5 over expression of SEQ ID NO 1 relative to expression of SEQ ID NO 1 in an uninfected central nervous system control sample from another mammal of the same species.

It is noted that applicant elected overexpression of Cripto-1, which is SEQ ID NO 1 of the instant claims.

The claims are drawn detection in "any" mammal, although claim 17 draws the claim to humans. Thus the claims broadly encompass detecting the SEQ ID NO 1 in dog, cat mouse, whale, etc and comparing to "any" central nervous system control sample.

Claim 19 is drawn to wherein RT-PCR is carried out using SEQ ID NO 3 and SEQ ID NO 4.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches in example 2 a study of 5 pig tailed Macaque. The study compares the expression of RNA isolated from the parietal cortex of 1 control uninfected Macaque with expression from 4 macaque infected with SHIV by use of human cytokine cDNA array (see paragraph 0073). The specification further teaches,

"A more stringent 2.5 difference was chosen as an arbitrary cutoff value for differences in gene expression." (See paragraph 0073). The specification further teaches the relative expression was calculated by use of normalization spots and standard housekeeping genes.

The specification teaches in Table 2 there was a 9.56 fold increase in Tetracarcinoma-derived growth factor (Cripto-1) in the cerebral cortex of exsanguinated 4 SHIV infected macaque relative to the uninfected macaque.

The specification teaches, "The function of Cripto in neurons in the adult brain and its up regulation in the brains of SHIV-infected macaques are also unknown" (see paragraph 0086).

Presence and absence of working examples

The specification teaches a single study involving 4 SHIV infected macaque and 1 non-infected control in which macaque homologs of nucleic acid that hybridize to SEQ ID NO 1 reagents are up regulated. However, this study uses a single control that has not been infected with any virus. Further this study examines tissue that has been collected post-exsanguinations and thus altered expression may merely be differences in the handling of the one control sample. This study does not teach detection of SEQ ID NO 1, but the macaque homologue of SEQ ID NO 1.

The specification does not teach any working examples of diagnosis based on detection or over expression of SEQ ID NO 1. The studies of the specification are drawn to detection of the macaque homologue of SEQ ID NO 1. The specification does not teach detection of SEQ ID NO 1, but the use of a human cDNA array and primers to

the cripto-1 human sequence to detect the macaque homolog of SEQ ID NO 1, which is different than SEQ ID No 1 as discussed in the state of the art section below.

The specification does not teach any studies in humans.

The state of prior art and the predictability or unpredictability of the art:

Sequence analysis by blast (blast.ncbi.nlm.nih.gov/Blast.cgi, 9/4/2008, pages 1-32) teaches that SEQ ID NO 1 is not the macaque cripto gene but has regions of 95% identity, but numerous gaps and regions with as little as 76% identity. Thus the BLAST analysis teaches that SEQ ID No 1 is not the macaque Cripto-1 gene and presumably was not being detected in the macaque models. Thus it would be unpredictable to associate the expression of a SEQ ID NO 1 with detection of a NeuroAIDS as the specification does not teach detection of SEQ ID NO 1, but amplification of a macaque homolog that is amplified by primers to a fragment of the human cripto-1 gene or genes that hybridize to a probe for the human Cripto-1 cDNA.

Benner et al (Trends in Genetics (2001) volume 17, pages 414-418) teaches that, "Here, the 'homology-implies-equivalency' assumption is restricted to a subset of homologs that diverged in the most-recent common ancestor of the species sharing the homologs. This strategy is useful, of course. But it is likely to be far less general than is widely thought. Two species living in the same space, almost by axiom, cannot have identical strategies for survival. This, in turn, implies that two orthologous proteins might not contribute to fitness in exactly the same way in two species" (see page 414, 3rd column last full paragraph). Benner specifically describes that although the leptin gene homologs have been found in mice and humans, their affect is different (see page 414,

3rd column last paragraph-3rd column page 415). Benner specifically teaches that the leptin gene in mice plays a major role in obesity, but no such effect has been demonstrated in humans due perhaps to the different evolutionary forces. Benner thus teaches that the activity and function of genes in different species is unpredictable.

May et al (Science (1988) volume 241, page 1441) teaches there are millions of known taxonomic species (table 3). May further teaches there are at least 4,500 known mammalian species (table 3).

Caceres et al (proceedings of the National Academy of Sciences (2003) volume 100, pages 13030-13035) teaches "we have identified 169 genes that exhibited expression differences between human and chimpanzee cortex, and 91 were ascribed to the human lineage using macaques as an outgroup" (abstract). Caceres teaches examination of 290 genes that differed between chimpanzees and humans 221 showed a human specific pattern of hybridization and 211 of the 221 had greater intensity in human samples (13033, 1st column). Carceres further teaches that there is a higher degree of divergence between human and rhesus sequence, thus making interpretation of microarray data less reliable (13033, 2nd column).

Roberts et al (American Journal of Pathology (2003) volume 162, pages 2041-2057) teaches a study to examine differential regulation of gene expression in macaques' brains by SIV infection. Roberts teaches 98 genes were identified, with 66 genes up regulated in the occipital lobe, 68 up regulated in the midbrain and 19 in the cerebellum (2047, 2nd column). Roberts teaches in table 2, 98 genes up regulated and does not identify SEQ ID NO 1. Roberts further notes that gene regulation is appears to

dependent on the location of the neurons relative to the infection (2055, 2nd column). Thus Roberts did not find the SEQ ID NO 1 was up regulated in macaque models of NeuroAIDS and further noted that gene expression patterns are dependent on the location from which the sample is take.

It is relevant to point out that the post-filing art of Cheung et al (Nature Genetics (2003), volume 33 pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a phenotype.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology (2001) volume 195, pages 53-65). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular

choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion).

Raghavan et al (Brain Pathology (1997) volume 7, pages 851-861) teaches a comparison of SHIV infection on pig tailed macaque compared to rhesus macaque. Raghavan teaches, "Our data show a clear contrast in the neuropathogenesis of SHIV infection in pig-tailed and rhesus macaque (page 858, 2nd column, 1st paragraph). Raghavan teaches that the pig tailed macaque the virus failed to become active, while in the rhesus macaque there was lentiviral replication which was accompanied by brain legions (page 858, 2nd column). Thus it would be unpredictable to correlate the expression of a gene in one species of macaque with any other mammal when Raghavan teaches the SHIV has different affects on two members of the macaque family and is thus unpredictable in macaques. Raghavan teaches the SHIV infection differed from the SIV infection of the brain as SHIV infected macaques lacked meningeal inflammation that is observed in SIV. Raghavan suggests the SIV and SHIV induced NeuroAIDS have different pathologies. Thus it would be unpredictable to associate a finding based on one virus known to cause NeuroAIDS, when Raghavan teaches these are differences in responses.

Further, Enard et al (Science (2002) volume 296, pages 340-343) teaches that intraspecies variation in gene expression in brain tissue is substantial (page 340, 3rd column). Enard continues, "One human brain sample differs more from the other human samples than the latter differ from the chimpanzee samples. However, for both

the brain and liver samples, the humans, as well as the chimpanzees, fall into two mutually exclusive groups when their gene expression patterns are related to that seen in the orangutan, which is evolutionarily further, removed from humans and chimpanzees than these are from each other." Thus it would be unpredictable in view of Enard to extrapolate the teachings based on a single control in one species due to the intraspecies variability in gene expression in brain, but it would be further be unpredictable to do such extrapolation to other mammals, as there is great variability between primates as demonstrated by differences between orangutan, chimpanzees, and humans. Further comparison of chimpanzees to human and macaque resulted in a 5.5 fold difference in expression. Thus it would be unpredictable to extrapolate the findings of a single finding using a single macaque as a control when the art teaches there is substantial intraspecies variation and suggests it would further be unpredictable to make interspecies comparison based on the teachings of Enard.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed one of skill in the art would first have to determine if a predictive relationship over expression of SEQ ID NO 1 in the central nervous system of a mammal relative to a sample from the uninfected nervous system of another mammal of the same species. This would be unpredictable as the specification teaches a single study of 4 macaques infected with SHIV compared to a single control that was not infected. A single experiment with such a small size sample

cannot be reasonably extrapolated to any mammals, as discussed further below. First the specification used primers and /or probes to human cripto-1, which is SEQ ID No 1, however the studies were done in macaque and would not have detected SEQ ID NO 1, but the macaque homolog, which is quite different as demonstrated by the BLAST alignment. Further the expression of the cripto-1 homolog may be a result of the viral infection, exsanguinations, or handling of the sample as gene expression in general is variable and the specification teaches macaque are out bred models, suggesting greater variability in gene expression patterns.

The artisan would have to determine if the instant method is predictable in any mammal. This would require undue trial and error experimentation as the specification teaches a single experiment in macaque monkeys. It would be unpredictable to extrapolate the findings of differential expression of a gene in one species with another as Benner teaches that due to different evolutionary pressures gene homologs in different species have different functions. Further it would be unpredictable as Caceres and Enard teach that the brains of the macaques, chimpanzees, and humans have different gene expression patterns. Thus it would be unpredictable to use the expression level of a gene in one species as diagnostic in another species, without specific evidence as even the closely related primate species have differential expression patterns in the central nervous system.

Further practicing the invention as claimed would require undue trial and error experimentation as the claims are drawn to "any" central nervous system tissue. The teachings of Roberts demonstrate that the different regions of the macaque brain have

differential expression patterns based on anatomical location and suggest that this expression is due to proximity to active infection. Thus based on the teachings of Roberts it would be unpredictable to extrapolate the findings of the instant specification in that the macaque homologue of SEQ ID NO1 is up regulated in the cortex of macaque as diagnostic in any other central nervous system tissue without specific evidence due to this variability.

Further the skilled artisan would have to determine if "2.5 fold overexpression" is required to result in a predictable association of SEQ ID NO 1 over expression and NeuroAids. This would be unpredictable as the specification teaches a single study with 1 control and 4 infected macaque. Cheung teaches that there is a 17 fold natural gene variation among individuals, thus the teachings of Cheung suggests the non-treated macaque may simply be an outlier.

In view of teachings of the art as to the variability of expression data as a whole, the limited population studied, and the use of a single control, the skilled artisan would have to undertake unpredictable and undue trial and error experimentation to determine if such a relationship exists in mammals. This would be unpredictable as in the single study taught by the specification SEQ ID NO 1 was not detected, but macaque homologs that hybridize to reagents for SEQ ID NO 1.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable

experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response on page 5 provides a short summary of the enablement issues of the previously presented claims.

The response in the second full paragraph begins arguments by directing the examiner to the declaration of Dr. Berman that the expense of macaque studies requires an art accepted use of smaller studies than rodent models. The examiner appreciates the differences in the expense of the different model systems used in biomedical research, and that the cost allows for smaller sample sizes in these studies. However, the instant claims are drawn to detection of NeuroAIDS in any mammal by a 2.5 fold increase in expression in a central nervous system sample of SEQ ID NO 1. The specification provides that a single control was used, however art of Cheung teaches there is 17 fold variability in gene expression within a species and subjects. Thus it would be unpredictable to use a single sample as a control for a diagnostic claim, without evidence that the single control is not a statistical outlier.

The response continues by asserting as suggested in the declaration of Dr. Berman that exsanguinations was done reliably and has not affected gene expression. While the declaration of Dr. Berman suggest that the exsanguinations does not result in variability between samples from the macaque, it does not provide that exsanguinations does not affect expression of SEQ ID NO1 in a sample from a live mammal relative to a

dead mammal or how the artisan efficacy of taking a biopsy from the cerebral cortex of a human.

The response continues by asserting that Dr. Berman explains one of skill in the art would recognize the primers to human SEQ ID NO 1 would identify gene expression of SEQ ID NO 1 and notes that human and macaque are not identical. The examiner concurs that the artisan could determine that primers for detection of SEQ ID No 1 may allow for detection of the macaque homologue. However, the claims require "assaying the expression level of SEQ ID NO 1." Thus the arguments to macaque homologue are beyond the scope of the claimed invention. The claims require assaying the expression of SEQ ID NO 1, not a homologue as asserted.

The response continues with point 8 of Dr. Bermans declaration noting the obstacles and invasiveness of altered gene expression in humans relative to animal models. The examiner concurs that animal models are important models of human disease, however the instant claims are drawn to detecting NeuroAids in any mammal and thus is considered a diagnostic. Thus due to the variability in gene expression between humans, macaques, and chimpanzees taught by Enard and Caceres it would be unpredictable to use altered expression in one species of primate for a diagnostic in any other species of primate without evidence that such over expression is diagnostic. It is further noted that the claims are not limited to primates, but any mammal which encompasses 4,500 species according to May, which have presumably even greater variations in gene expression. Further there is no evidence that any species other than

humans express SEQ ID NO 1, nor evidence that over expression of SEQ ID NO 1 in humans is predictably diagnostic of NeuroAids.

The response continues to point 10 of Dr. Bermans declaration that Stephens et al Neuroscience Lett 410:94-99 (2006), Buch Neuroimmunol 157:71-80 (2004), Sui et al J Med Primatol 32:229-239 (2003) used similar methods to those of the instant specification. The examiner concurs these publication demonstrate that similar methods have been used in peer reviewed publication. However, publication in a peer reviewed journal does not demonstrate the study or method used in the study is patentable. Further, Stephens concludes,"Whether cripto-1 expression is elevated during the course of NeuroAids due to enhanced expression of one or more cytokines/chemokines" (98). Thus the post-filing art of Stephens and inventors of record do not suggest that over expression of SEQ ID NO1 is diagnostic of NeuroAids, but still is questionable.

The response then moves to the art of Williams to demonstrate that SIV and SHIV models are essential models for the study of human NeuroAids. The examiner agrees that importance of animal models in medical research. However, the claims are not drawn to methods of studying NeuroAids, but detection or diagnosis of NeuroAids in any mammal. Thus the arguments to the importance of animal to models is beyond the scope of the claimed invention as it does not demonstrate that detection of expression of nucleic acids from macaque that hybridizes to probes directed to SEQ ID NO 1 allow for diagnosis in any species.

The response refers to art in Williams that post-dates the teachings of Stephens suggesting the importance of macaque models in human NeuroAids research. These arguments have been addressed above, however, further review of Williams demonstrates that there are differences that in the human syndrome and animal models. Williams teaches that "Unlike the human syndrome, in SIVmac251-infected macaques, inflammatory lesions in the meninges and neuropil occur in the presence of relatively normal numbers of CD4+ T lymphocytes in peripheral blood, although CD4+ T cells frequently "crash" during progressive neurological disease." Williams continues, "unlike the human CNS disease, SIV lesions in the CNS are much more severe compared with those seen in HIV-infected brains. These differences can be attributed to the natural history of HIV infection in which CD4+ T cells are lost prior to development of neurological symptoms, whereas in macaques, the CD4+ T cells may contribute to the development of lesions" (294, 1st column-2nd column). Williams continues of page 295, "Although SIV-infected macaques have been critical in our understanding of lentiviral neuropathogenesis, the genetic relatedness of these viruses is more to HIV-2 than HIV-1, especially in the env gene, which raises the question of whether these models accurately mimic the neuropathogenesis of HIV-1 infection." Thus although Williams teaches the macaque model is important in the study of NeuroAIDS, Williams notes there are differences between HIV and SIV models, which suggest differences in pathologies and unpredictability between models. Further Williams does not provide any guidance on detection of NeuroAids in humans based on macaque disease.

The response and declaration point 11 continue by noting that a nexus need not be provided for a particular gene and a disease state. The examiner agrees that often genes are identified as involved in a disease state, before the relationship of the disease state is understood. However, the instant specification has not provided that the SEQ ID NO 1 expression is indicative of a disease state, as it only detects a homologue, which is different than the invention claimed.

The response/declaration continues to point 12 by asserting that Dr. Berman explains the differences between SIV and SHIV the pig-tailed and rhesus monkeys described as Raghavan as rhesus macaques activate the virus. The response further notes that Raghavan is silent due to the effect of activation or inactivation of SHIV on Cripto 1 expression. These arguments have been thoroughly reviewed but are not considered persuasive as the Raghavan teaches there was CNS infection on both rhesus and pig tailed macaque (857). Thus the different pathologies demonstrate that even closely related species infected with SIV had different effects. Thus it would be unpredictable to use the finding in a one primate for diagnosis in another primate, when Raghavan teaches they have different pathologies due to infection with the same virus.

The response and declaration go on to point 13 to assert that SHIV model in macaque would be an acceptable model for NeuroAIDS in humans and thus overcome the issues of Enard and Cheung. These arguments have been thoroughly reviewed but are not considered persuasive as the claims are not drawn to models of NeuroAids but detection of NeuroAids. The teachings of Enard and Caceres demonstrate there is interspecies variability between even the closely related primate species and humans.

Further the teachings of Cheung to the expression variation of up to 17 fold demonstrates that multiple controls would be required to determine that an over expression observed in not due to an outlier.

The response continues to point 14 of the declaration in which Dr. Berman notes that Buch and Sui used similar method to the instant specification and then argues the teachings of Wu, Newton, and Vandesompele. First the arguments to Wu, Newton, and Vandesompele have been withdrawn by the examiner. While the teachings of Buch and Sui do describe similar methods the discussion of these articles provide evidence of the unpredictability.

First in the abstract, Buch teaches that HIV infects using CXCR5 receptors, while SHIV uses CXCR4 receptors (abstract). Buch teaches that the use of X4 virus are strictly T cell tropic in macaque and their role human infection are unknown. Thus the infections have different mechanisms and targets in different species. Buch points to the teachings of Raghavan and states," It was remarkable that only rhesus macaques and not pigtailed developed X4 SHIVKU2 associated neurological disease"(72, 2nd column, lat paragraph). Thus again reiterating that all species do not respond to SIV or SHIV infection with the same pathogenesis. Buch then presents 40 genes up regulated by SHIV infection of macaques in table 1, but did not find SEQ ID NO 1 (cripto1) to be one of these genes. Thus suggesting that SEQ ID NO 1 is not predictably up regulated in NeuroAids,

The teachings of Sui, which is referenced by Buch, teaches total RNA was isolated from the basal ganglia region of the brain and gene expression analysis was

performed (231, 1st column). Sui teaches that comparison of expression from 2 control animals relative to the infected revealed 50 genes that were up regulated , but again Cripto1 was not detected(233, 2nd column and table 1).

The response and declaration conclude by asserting that an ordinary artisan would understand the specification enables methods of detecting NeuroAids in a mammal by detecting cripto1. These arguments have been thoroughly reviewed but are not considered persuasive as the claims are drawn to detecting expression of SEQ ID NO 1, not cripto1 as asserted. The response has provided no evidence that SEQ ID NO 1 can be detected in any species other than humans from which it was cloned nor provided that a 2.5 fold increased in expression of SEQ ID NO 1 relative to a non-infected control CNS sample allows for detection of NeuroAids. The response and declaration teach, "macaque and human Cripto1 gene are not identical" (point 8). Thus it would be unpredictable to use detection of SEQ ID NO 1 to detect a disease in any other species, when the neither instant specification nor prior art have detected expression of SEQ ID NO 1 is diagnostic of any disease. Thus for the reasons of record the rejection is maintained.

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is

(571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Juliet C Switzer/
Primary Examiner, Art Unit 1634